

**A bioactive material with dual integrin-targeting ligands regulates specific endogenous cell adhesion and promotes vascularized bone regeneration in adult and fetal bone defects.**

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**Public Summary:**

Significant progress has been made in designing bone materials capable of utilizing a patient's own cells to promote bone healing and regeneration. However, current strategies lack regulation of the specific cell types that can result in non-typical tissue regeneration patterns and decreased regeneration efficacy. In this study, we engineered a biomaterial that encourages cell adhesion to affected areas and increased bone regeneration. The biomaterial was constructed by joining two molecules, LLP2A and LXW7, to a collagen-based scaffold to increase the binding capacity for cells that secrete factors involved in bone healing and neuron protection. LLP2A and LXW7 have a high binding affinity for integrin proteins,  $\alpha_4\beta_1$  and  $\alpha_v\beta_3$ , on the surface of cells that encourage bone healing, such as mesenchymal stem cells (MSCs), osteoblasts, endothelial progenitor cells (EPCs), and endothelial cells (ECs). MSCs and EPCs are capable of differentiating into multiple cell types and secrete factors that increase cellular regeneration of cells like ECs, which are important for the growth and development of connective tissues. An adult rat skull bone defect model and a fetal sheep spinal bone defect model were used to evaluate the ability of the biomaterial to bind MSCs and EPCs. In both models, the LLP2A/LXW7 modified biomaterial enhanced bone formation and new vessel formation by targeting and binding cells with bone and vascular growth potentials. This innovative biomaterial offers an off-the-shelf, easy-to-use, and biologically safe product suitable for vascularized bone regeneration in both fetal and adult disease environments.

**Scientific Abstract:**

Significant progress has been made in designing bone materials capable of directing endogenous cells to promote vascularized bone regeneration. However, current strategies lack regulation of the specific endogenous cell populations for vascularized bone regeneration, thus leading to adverse tissue formation and decreased regenerative efficiency. Here, we engineered a biomaterial to regulate endogenous cell adhesion and promote vascularized bone regeneration. The biomaterial works by presenting two synthetic ligands, LLP2A and LXW7, explicitly targeting integrins  $\alpha_4\beta_1$  and  $\alpha_v\beta_3$ , respectively, expressed on the surfaces of the cells related to bone formation and vascularization, such as mesenchymal stem cells (MSCs), osteoblasts, endothelial progenitor cells (EPCs), and endothelial cells (ECs). In vitro, the LLP2A/LXW7 modified biomaterial improved the adhesion of MSCs, osteoblasts, EPCs, and ECs via integrin  $\alpha_4\beta_1$  and  $\alpha_v\beta_3$ , respectively. In an adult rat calvarial bone defect model, the LLP2A/LXW7 modified biomaterial enhanced bone formation and vascularization by synergistically regulating endogenous cells with osteogenic and angiogenic potentials, such as DLX5(+) cells, osteocalcin(+) cells, CD34(+)/CD45(-) cells and CD31(+) cells. In a fetal sheep spinal bone defect model, the LLP2A/LXW7 modified biomaterial augmented bone formation and vascularization without any adverse effects. This innovative biomaterial offers an off-the-shelf, easy-to-use, and biologically safe product suitable for vascularized bone regeneration in both fetal and adult disease environments.